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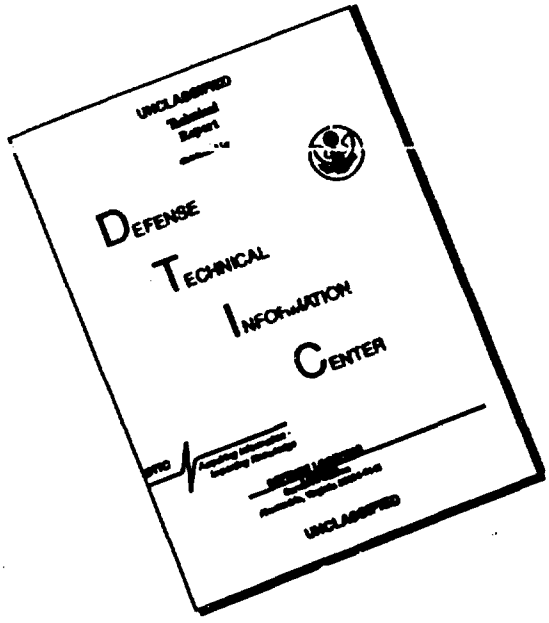

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KINDERGARTEN EPIDEMIC CAUSED BY ADENO-VIRUS 7

(The following is an article by P. Osvath and M. Troth, published in the German language periodical, Arch. fur Kinderheilkunde (Archives for Childrens Well-Being) Vol. 172, July 1965, pages 268-75. Translation performed by Constance L. Lust).

Adeno-virus 7 is the cause of infections of the air passages (1, 13, 17, 20, 26, 28). The epidemiological characteristics of the spread of adeno-virus infections of the airpassages have most often been described in connection with epidemics occurring among army recruits (3, 12, 24). According to the observations of Hillemann (12), 80% of the recruits can be proved to have had the disease with serological methods, but actual symptoms appear in only 40%, the infection running its course without being detected in the rest. It is much more difficult to study the spread of air passage-infections caused by the adeno-virus 7 in communities of healthy children, and for this reason we believed the following observations to be worthy of publication.

Methods

The nose and throat secretions of the children studied were obtained with swabs, and were immediately injected into sterile Parker-199 solution containing an antibiotic and the isolating material was then added simultaneously to two cultures; primary monkey kidneys and "He La" agar. Seventeen of the 20 strains isolated grew in both cultures, but 3 grew only in the "He La" cultures. The viruses were identified through neutralisation with strain-specific immunising serum.

Of the serological procedures we utilised the "Complement fixation test" (10). As is known, the adeno-viruses contain a common soluble antigen, so that all that can be determined from changes in the titer values in the reaction is that an infection had occurred.

We determined the strain of the virus by using the hemagglutination-retarding antibody-titer change of Rosen (22, 23). The essentials of this procedure are that the adeno-virus causes an agglutination of the red blood cells of monkeys. This agglutination is prevented with a specific immunising serum. The dilution series of the serum to be tested was incubated with virus of a pre-determined titer value. After one hour of standing at room temperature, a 1% solution of monkey blood cells was added to the mixture, which was then incubated for another hour at 37 degrees C. The serum containing the immunising agent retards the hemagglutination, and the titer value of this retardation is determined.

The epidemic to be considered occurred in January, 1964 in a suburb of Budapest. There were 36 children ranging in age from 3 to 7 in the kindergarten. Virological examinations were carried out on 22 of them, all of whom showed clinical evidence of more or less serious infections of the air passages. Ten of the 14 children were not ill at the time of our examinations, and the last 4 were ill, but we were unable to carry out the necessary tests. One of us (Osvath) was the pediatrician of the community as well as of the kindergarten, and was thus able to control the children at home as well as at school.

Results

In December of 1963 there was a varicella epidemic in the kindergarten. The children were re-admitted only after medical examination. The first sporadic air passage infections appeared at the beginning of January. The number of absences due to illness rose quickly from the seventh of January and reached its apex on January 10, when almost one half (14) of the children were out. The material for the virological examination (nose-and throat secretions, blood) was obtained on January 17, when approximately 25% of the children (10) were still in bed, and 6 still showed certain clinical symptoms, even though the acute phase of the infection was passed. Ten children came to the kindergarten in spite of air passage infections. The second blood test was taken on January 31, when the epidemic was over. Only one child was still ill, and it was to spend the entire month of February in the hospital with pneumonia. The infection spread rapidly. Between January 2 and 17 all the susceptible children, with the exception of two, fell ill, and those two did already show clinical symptoms on the seventeenth, even though the more serious phase of the infection requiring bed care only began later (see illustration 1).

Virological examination resulted in the isolation of the adenovirus 7 (see table 1) in 19 of the 44 cases, and type 3 was isolated in only one culture.

The causative agent could be cultured from both nose and throat secretions in six of the fourteen virologically positive cases, and although no viruses could be proved to exist in the other eight cases the significant rise in antibodies retarding the hemagglutination of adeno-virus 7 proved three of these to have the same etiology. In another three cases the serological reaction with high or rising titers also indicated the probability of a similar causative agent (case no. 18, 19, 20). This, then, leaves two patients in whom the adeno-7 infection could not be proved. It is unlikely that the adeno-3 virus played a larger role in the epidemic, since there were only two cases in which the titer values rose significantly.

Besides the tests listed in the table, we also treated for antibodies producing bacteriolysis with the antigens of the influenza viruses A, A2, and B, but significant changes appeared in only 4 cases, and

even these were reacting to different types. If an influenza epidemic had occurred simultaneously with the adeno-7 infection, we would have had to see changes in titer values in a great many more cases, according to the experience of Vivell (35).

The subjective symptoms of the sick children were above all coughing and moderate fever (maximum of 39 degrees C), as is shown in illustration 2. The conjunctivitis was very mild in all cases. The relationship between rhinitis and lymphadenopathy was greater than was to be expected on the basis of information from the literature (30). Inflammation and granulation of the forward gums occurred in eight cases, besides pharyngitis; in contrast to this the adjacent tonsils were clearly very seldom affected. In no case did the bronchitis have spastic characteristics. The pneumonia was mild with the exception of one case and manifested itself only in physical signs - sometimes in widespread crepitation - but never caused dyspnea. X-rays were made in three cases, but the results showed no signs of infiltration.

The patients were given various antibiotics, none of which had any effect on the course of the illness. After the passing of the acute phase, many of the children still showed signs of bronchial rattling and even of crepitation, in spite of the fact that they no longer had a fever and their parents no longer considered them to be ill. Table 2 shows the relationship of the place of virus isolation and the clinical symptoms to the length of the illness. It clearly shows, that the virus could only be isolated in the nose of those children who had just fallen ill, whereas all those in whom the virus was isolated only in the throat had been ill for more than a week. This could be related to the fact that coryza is already more unusual after a week, while the inflammation of the lower air passages still exists.

The clinical symptoms lasted about 14 days, but the febrile phase, which was serious enough to require bed care in all cases, generally lasted only 7 days.

In Hungary adeno-virus isolation was first attempted in 1958 by Beladi and Kahan (2) as well as Nasz, Toth and Lengyel (19). In 1963 Boda and his colleagues (6) reported a larger number of cases of pharyngo-conjunctive fever from a hospital. Until now, no epidemic caused by the adeno-7 virus has been observed in Hungary. As regards the probability of past infection among the population, Nasz and Toth give evidence (18) that indicated the existence of antibodies to neutralise the virus in 30% of the children under 10 years of age.

The children affected by the epidemic we discussed formed a fairly closed community. In this region the children hardly came into contact with persons outside their immediate families and used no public

transportation to reach the kindergarten. This explains how an epidemic with such a homogeneous etiology could occur in a group not living in a public institution. The immunological status of the children was also similar to a large extent: with the exception of two, all of them had a negative adeno-7 HAG titer at the beginning of the epidemic. This created conditions for the spread of the infection that are otherwise only obtainable in the experimental infection of volunteers (4). This probably explains why the incidence of infections was substantially greater than in the epidemics in nursery schools observed by Chany and his colleagues (7) and by Kendall (16).

The high rate of contagion led to the suspicion of infection with influenza virus in the clinical diagnosis of the epidemic. In the diagnosis of air passage infections that present a similar clinical picture, knowledge of the spread of the epidemic can be useful (11, 21). The lower morbidity rate is considered characteristic for adeno-virus epidemics in view of the large number of inapparent infections (12, 28, 30). But it appears that in groups of children without previous immunity the majority of infections appear as manifest illnesses, even in the case of air passage infections caused by adeno-virus. Even during the course of the epidemic there was considerable data indicating the probability of an adeno-virus infection: for example, the mild effects as compared with influenza, and the lymphoid hyperplasia which occurs much more often in infections of the air passages due to adeno-virus than in grippe, according to Schultze and his colleagues (25). Adeno-virus infection was also indicated by the fact that the adults in the kindergarten were not affected - as in the epidemic reported by Sobel and his colleagues (26).

The clinical symptoms observed in the children were completely in accord with those presented by Hamre and Budde (17) in their comprehensive report. However, the gastroenteritic symptoms (27) and the more severe conjunctivitis (15, 30) described in the Scandinavian countries were not present here.

Many references in the literature consider the atypical pneumonia, indicated only in x-rays, as characteristic for adeno-virus infections (12, 17, 30, 24, 34), probably because the majority of cases observed occurred among young adults. However, Chany and his colleagues (5, 7), as well as Tsu Ching (8, 31), discovered substantial rattling noises as well as x-ray changes that were at first quite minor in cases of adeno-virus-pneumonia of a serious nature among young children. Sterner (29), Clarke and his colleagues (9) and Vargosko and his colleagues (33) have all described milder cases of adeno-virus pneumonias among children which could be proved by culturation, similar to the cases we observed. The majority of these cases was observed in hospitals and can therefore not be used as a basis for determining what percentage of adeno-virus infections among children cause pneumonia, as was pointed out by Sterner (30). The kindergarten epidemic reported by us provides new statistics towards answering this question. In 9 of the 26 affected children - that is, in approximately on third of them - we observed symptoms indicating pneumonia. A similar rate of incidence for pneumonia was

also observed by Hillemann and his colleagues (12) in an adeno-virus epidemic that occurred among recruits and by Jansson and his colleagues (14) in connection with their hospital observations.

Our observation, that there is a relationship between the length of the illness and the place in which the virus can be isolated indicates that viruses of the adeno-7 type first locate in the nasal cavity, but are hardly ever found there when the rhinitis is no longer present and the bronchitis symptoms predominate. At this point they are easily located in the throat however, which they presumably reach together with bronchial secretions which are brought up by coughing.

Brief Review

Report of a kindergarten epidemic caused by adeno-7 virus and manifesting itself with symptoms of the air passages. Seventy two per cent of the children in the community fell ill with a mild or moderately serious infection of the air passages. It was possible to isolate the virus in 14 of the 22 cases tested virologically. In another 6 cases the conversion of the "HAG" or "Compliment fixation test" indicated the probability of an analogous etiology. This made it possible to show the course of an adeno-7 infection which showed manifest clinical symptoms as well in 55% of the children.

In 35% of the cases a mild pneumonia which appeared mainly in evidence obtained from cultures was determined. In the remaining cases the infection appeared as a bronchitis or rhino-pharyngitis.

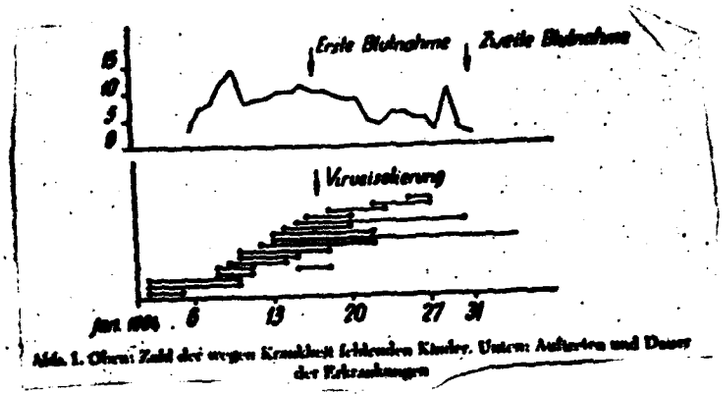

Abb. 1. Obere: Zahl der wegen Krankheit fehlenden Kinder. Untere: Auftreten und Dauer der Erkrankungen

Figure 1 - (upper) Number of children missing because of illness
(lower) Appearance and duration of illnesses.

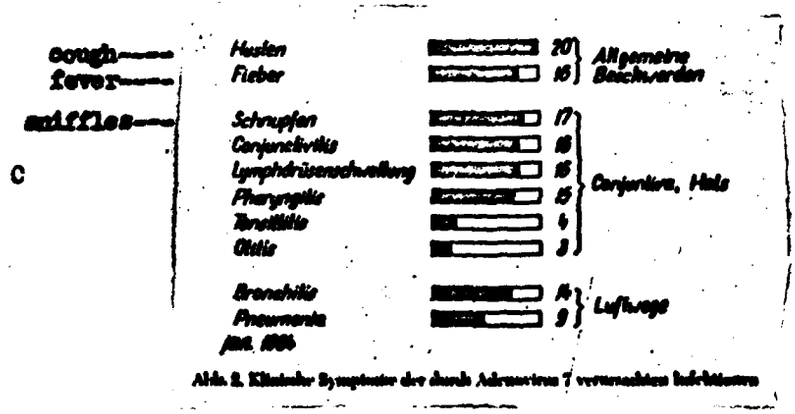

Abb. 2. Klinische Symptome der durch Adenovirus 7 verursachten Infektionen

Figure 2 - Clinical Symptoms of the illnesses caused by adeno-virus 7

Table 1

Results of the virus isolation and the serological tests

Name — Age — Day after illness — virus isolated nose — throat — Antibody for adeno-virus

Tabelle 1. Ergebnisse der Virusisolierungen und der serologischen Untersuchungen.

Name	Alter	Tag nach dem Beginn d. Krankheit am 17. Jan.	Virusisolierung Nase	Rachen	Antikörper gegen Adenovirus Hämagglut. hemmende Compl. Adenus 9 I. 17.	I. 31.	Adenus 7 I. 17.	I. 31.	bindende I. 17.	I. 31.
1. B. I.	6 Jahre	1.	Ad 7	Ad 7	0	0	0	32	8	16
2. H. J.	3 „	9.	Ad 7	Ad 7	256	256	128	256	8	16
3. V. K.	6 „	2.	Ad 7	Ad 7	—	—	—	—	4	—
4. R. K.	5 „	4.	Ad 7	Ad 7	0	0	0	16	0	4
5. N. J.	5 „	10.	Ad 7	Ad 7	0	0	8	32	64	64
6. P. K.	7 „	1	Ad 7	Ad 3	0	32	0	16	128	32
7. P. N.	7 „	1	Ad 7	neg	0	0	0	32	32	128
8. C. J.	5 „	1	Ad 7	neg	0	0	0	16	0	8
9. F. P.	4 „	1	Ad 7	neg	256	256	64	256	0	0
10. L. O	5 „	1	Ad 7	neg	64	256	32	128	8	128
11. R. F.	6 „	6.	Ad 7	neg	0	0	0	16	8	32
12. T. L.	5 „	8.	neg	Ad 7	0	0	0	16	16	16
13. H. A.	5 „	15.	neg	Ad 7	—	—	—	—	8	32
14. S. A.	5 „	10.	neg	Ad 7	256	256	64	64	4	64
15. P. P.	6 „	?	neg	neg	64	32	32	256	0	4
16. J. A.	3 „	7.	neg	neg	0	0	0	32	8	8
17. R. K.	3 „	8.	neg	neg	0	0	0	32	0	0
18. R. U.	5 „	4.	neg	neg	—	—	—	—	64	—
19. T. K.	5 „	13.	neg	neg	16	16	16	32	16	16
20. J. L.	6 „	13.	neg	neg	16	16	16	32	32	4
21. P. Z.	3 „	4.	neg	neg	0	0	0	0	4	8
22. P. L.	5 „	10.	neg	neg	—	—	—	—	16	—

0 = ohne Antikörper. — = keine Untersuchung

0 = no antibodies — = not done

Table 2 - Localisation of virus isolation and clinical symptoms of those ill one week and longer

Region der Krankheit	Zahl der Fälle	Virus-Isolierung Nase	Virus-Isolierung Rachen	Klinische Rhinitis Ja	Klinische Rhinitis Nein	Symptome Bronchitis Ja	Symptome Bronchitis Nein
Nach dem 11. Januar	14	10	8	14	0	11	3
Vor dem 11. Januar	8	1	4	3	5	7	1

beginning — # — nose — throat — Clinical rhinitis yes no — Symptoms bronchitis yes no

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